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PERIPHERAL HEARING LOSS CAUSES HYPEREXCITABILITY OF THE INFERIOR COLLICULUS

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Abstract

Growing evidence has been found to suggest that early development of the central auditory system is dependent on acoustic stimuli. Peripheral damage caused by noise exposure and ototoxic drugs can induce functional and anatomical changes along the auditory pathways. The inferior colliculus (IC) is a unique structure in the auditory system located between the primary auditory nuclei of the brainstem and the thalamus. Damage to the IC inhibitory circuitry may affect central auditory processing and sound perception. Here, we review some of the striking electrophysiological changes in the IC that occur after noise exposure and ototoxic drug treatment. A common occurrence that emerges in the IC after peripheral damage is hyperexcitability of sound-evoked response. The hyperexcitability of the IC is likely related with reduced inhibitory response that requires normal peripheral inputs. Early age hearing loss can result in a long lasting increased susceptibility to audiogenic seizure which is related to hyperactivity in the IC evoked by loud sounds. Our studies suggest that hearing loss can cause increased IC neuron responsiveness which may be related to tinnitus, hyperacusis, and audiogenic seizure.

Key words: Inferior colliculus, noise exposure, salicylate, audiogenic seizure, tinnitus, hyperacusis

Introduction

The inferior colliculus (IC), a complex neural circuit in the auditory brainstem, plays an important role in sound processing. Damage to the IC inhibitory circuitry likely contributes to different hearing disorders including tinnitus and hyperacusis[1,6]. Previous studies in our lab have demonstrated that restricted cochlear lesions can cause massive functional changes in the IC. Hyperexcitability in a region of the IC may be triggered by noise exposure[12] or ototoxic drugs[18]. These changes may be related with inhibitory circuitry reduction or synaptic efficiency increase. In the following sections, we will summarize the IC function changes caused by peripheral damages due to noise exposure, carboplatin treatment, and early age hearing loss.

It has been proposed that peripheral hearing loss would reduce the local inhibition of the central auditory system, resulting in increased central neural responsiveness[8]. Since the central auditory system is enriched with inhibitory circuitry, damage in the cochlea can cause an increase, rather than a decrease, in the central auditory response, presumably due to reduction of the central inhibition. Aging and noise induced hearing loss often cause lesion to a small area such as the basal turn of the cochlea, which corresponds to a high frequency region. The cochlear damage in these regions may cause an increased gain in high frequency response. This also affects the tonotopic map of auditory cortex (AC) which may be a central source of tinnitus. The fact that perceived pitch of tinnitus is commonly equal to the frequency on the lower edge of the damaged frequency regions supports this theory. The tonotopic map changes may be caused by the uniformity of the inhibitory field in the central auditory system, such as the IC and the AC.

Noise Exposure Caused IC Function Changes

Peripheral damage caused by noise exposure can cause elevated responses in the auditory midbrain. Using chronically implanted recording electrodes on the round window, the cochlear nucleus (CN), and the IC, Salvi et al found that the input/output function of compound action potential (CAP) recorded from the round

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window in awake chinchillas shifted to the right by 10-15 dB one day after noise exposure (2.8 kHz tone presented for 2 hours at 105 dB SPL), reflecting a slight loss in sensitivity (Figure 1A)[17]. The amplitude of CAP also showed a significant reduction at moderate to high intensities consistent with the loss in sensitivity. The IC response to low intensity acoustic stimuli also reduced significantly after noise exposure. However, the IC response at the level above the threshold maintained the same or even increased (Figure 1B). The result suggests that noise exposure may impair inhibition from the damaged region. Wang et al. tested the acute change in IC neural response caused by noise exposure (narrow band noise) in anesthetized chinchillas[24]. They found that the excitatory response area of many neurons expanded to lower frequencies (Figure 1C) and the firing rate of those neurons tuned to low frequencies significantly increased after noise exposure (Figure 1D). The results suggested that neurons tuned to high frequencies became sensitive to low frequency acoustic stimuli after noise exposure. This change may be caused by damage to side-band inhibition in the IC[18]. Damage of side-band inhibition may increase the evoked potential amplitude of the IC at low frequency by increasing the number of neurons responding to these low frequency stimuli. This phenomenon suggests that peripheral damage not only reduces sound sensitivity to noise exposed frequencies, but may also cause increased sound sensitivity to frequencies at the lower edge of the damaged frequency range.

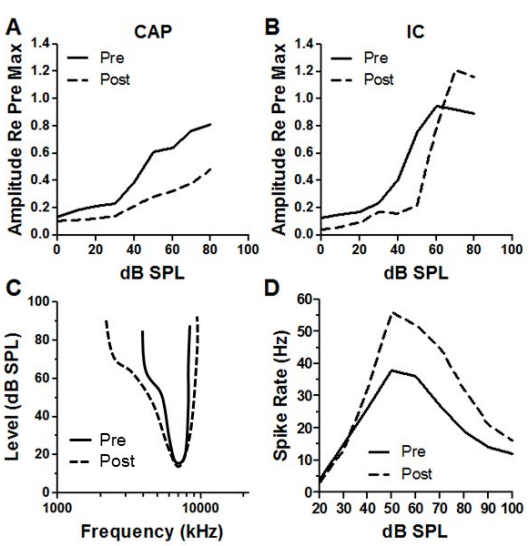

Figure 1. Noise exposure caused functional changes in the cochlea and the inferior colliculus (IC). (A) Rightward shift of the input/output function of the compound action potential (CAP) recorded from the round window of chinchillas caused by noise exposure. This reflects a slight loss in sensitivity. (B) Significant reduction of the IC response to low intensity acoustic stimuli caused by noise exposure. However, the IC response at the level above the threshold showed an increased response. (C) Expansion of the excitatory response area of the IC towards the lower frequencies and increased firing rates (D) caused by noise exposure

Recently, Ben Scholl et al. reported that acute acoustic trauma could induce an imbalance of excitation and inhibition in auditory cortical neurons[19]. They found that noise exposure caused a decrease of synaptic inhibition in the auditory cortex at low frequency ranges and an increase of synaptic inhibition at high frequency ranges. This study indicated that acoustic trauma might cause an asymmetrical damage in the inhibitory field in the auditory cortex. Noise exposure may impair side-band inhibition from the damage region at the lower frequencies of tested neurons.Since the lack of side-band inhibition had been hypothesized as a cause of the increased IC neuronal response, we tested the input-output function of the IC neuron located at different sides of the hearing loss regions to reveal how impairment of side-band inhibition affects the input-output function of the IC neurons. Interestingly, we found that high frequency noise exposure caused an expansion of the tuning curve towards lower frequencies, but not higher frequencies (Figure 2). However, the spontaneous activity in high frequency region showed a significant increase (Figure 2, arrows). These results suggest that noise trauma induced a decrease in synaptic inhibition at the low frequency range, not in the high frequency range. A recent study found that trauma-evoked tinnitus developed in the frequency range bordering the low frequency slope of the induced noise trauma[14]. This result supports the theory of lateral inhibition as the physiological basis of tinnitus. The spontaneous activity change caused by noise exposure in the high frequency range may be related with tinnitus perception after noise exposure[13, 16].

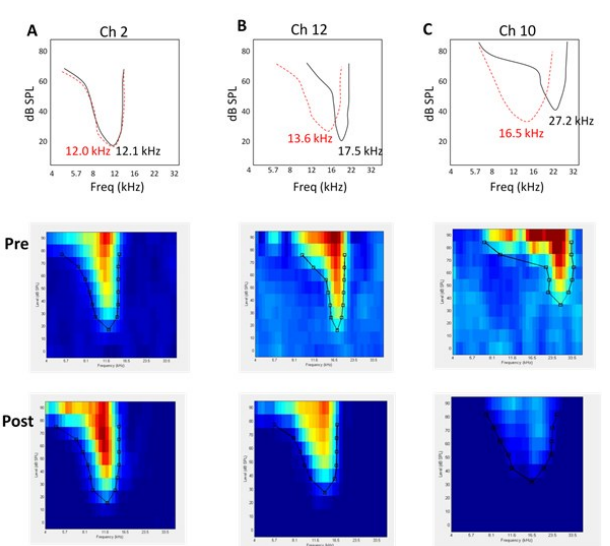

Figure 2. Tuning curves (the first row) and the excitatory frequency responses (the second and third rows) of inferior colliculus (IC) neurons in mice. (A) The characteristic frequency (CF) and mini-

mal threshold (MT) of a tuning curve center at 12 kHz showed no change before and after noise exposure; (B) The CF of a middle frequency neuron dropped from 17.5 to 13.6 kHz after noise exposure. Noise exposure caused a slight increase of the MT; (C) The CF of a high frequency neuron dropped from 27.2 to 16.5 kHz without MTs change.

Ototoxic Drug-induced IC Response Changes

Peripheral damage caused by ototoxic drugs, such as carboplatin and salicylate, can also affect the excitability of the central auditory system. Qiu et al. studied the functional changes of the IC after peripheral damage caused by carboplatin treatment in chinchillas[15], a unique animal model for inner hair cell damage[22]. They found that several weeks after two doses of carboplatin injections (38 mg/kg and 25 mg/kg intraperitoneally, one week apart), the amplitude of the cochlear response showed a significant reduction (Figure 3A)[15]. Post-test histology examination showed an average of 30-40% of inner hair cell loss across all frequencies on cochleogram. However, the local field potential of IC increased at a faster than normal rate and its maximum amplitude was enhanced at frequencies below the region of hearing loss (Figure 3B). This long term functional change of the IC response may be due to the synapse reorganization after the peripheral damage[18].

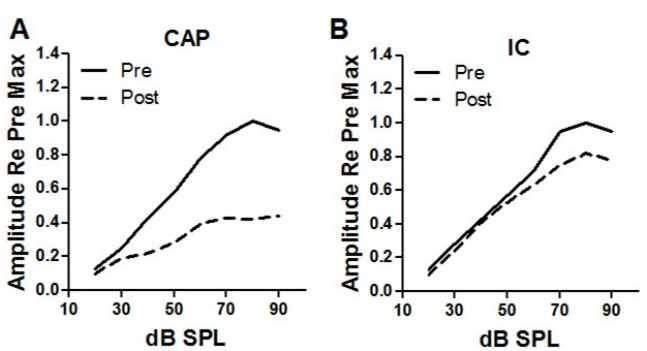

Figure 3. Carboplatin exposure caused functional changes in the cochlea and the inferior colliculus (IC). (A) The amplitude of the cochlear response shows a significant reduction after carboplatin treatment. (B) Local field potential of the IC increases at a faster than normal rate after carboplatin exposure.

Some ototoxic drugs can also cause changes in the central auditory system. Our recent studies found that salicylate injection (250 mg/kg, i.p.) reduced the CAP amplitude significantly (Figure 4A). The amplitude of IC response dropped rapidly to low level sound stimuli. However, at higher intensity levels, the amplitude of IC response remained at the same level compared to before salicylate injection (Figure 4B). This change is believed to be related with reduced GABA inhibition in the IC. Salicylate can block GABA inhibitory postsynaptic current in the IC[23]. This result suggests that reduced central inhibition can significantly affect the amplitude of central responses. Interestingly, after large doses of salicylate (250 mg/kg, i.p.), acoustic startle response amplitude at high intensities also increased significantly (Figure 4D)[20]. The enhanced acoustic startle response amplitude can be suppressed by an injection of baclofen, a GABA-B receptor agonist. These findings suggest that salicylate injection induced increases of central gain may increase central responses through inhibiting GABA mediated inhibitory pathways[11].

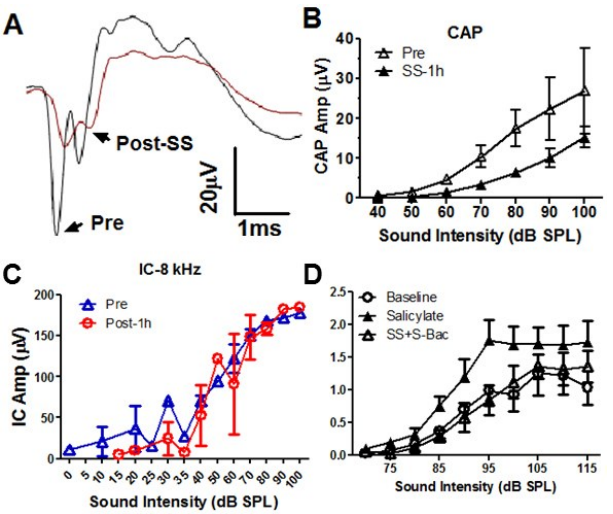

Figure 4. Effects of salicylate on auditory response. (A) Raw data of compound action potentials before and after salicylate injection (250 mg/kg, i.p.). Salicylate exposure caused a significant reduction of the CAP amplitude. (B) The input/output function of the CAP amplitude showed a significant decrease after salicylate exposure. (C) Salicylate did not affect the amplitude of IC responses at high intensities. (D) Salicylate injection increased acoustic startle amplitude. The enhanced acoustic startle responses caused by salicylate were suppressed by baclofen.

Early Age Hearing Loss Causes Hyperexcitability in the IC

Growing evidence suggests that central auditory system development is activity dependent[2,3]. Failure to receive proper excitatory input from the cochlea is known to cause functional impairment and sound processing deficits[25]. Previous studies found that early age hearing loss in rodents can increase the prominence of audiogenic seizure. For example, high intensity sound stimuli from ringing bells (~125 dB SPL) can cause wild running followed by erratic leaping, clonic convulsion, and even death in mice whose tympanic membranes were previously perforated[4,5,7]. To study how early age hearing loss affects central auditory function development, we have tested the effects of tympanic membrane dam-

age at an early age on sound perception development in rats[21]. Two weeks after tympanic membrane perforation at postnatal 16 days, more than 80% of the rats (n = 32) experienced audiogenic seizures when exposed to a loud sound (120 dB SPL white noise, < 1 minute). The rat's susceptibility to audiogenic seizure lasted at least sixteen weeks after tympanic membrane damage. The hearing threshold evaluated by auditory brainstem response tests showed no significant difference between the rats in the damaged membrane group and those in the control group (Figure 5A). However, ABR wave V-I interval of the damaged membrane rats was significantly shorter than that of the rats in the control group ($F = 17.46$, $p = 0.0004$, Two-way ANOVA, Figure 5B). At 100 dB SPL, the average wave V-I interval was 3.47 ± 0.07 ms (n = 4) and 3.31 ± 0.05 (n = 4) for the control and damaged membrane rats, respectively. These results suggest early age hearing loss caused by damage to the tympanic membrane will create a quicker neural transmission from the auditory nerve to the brainstem, rather than causing a delayed reaction.

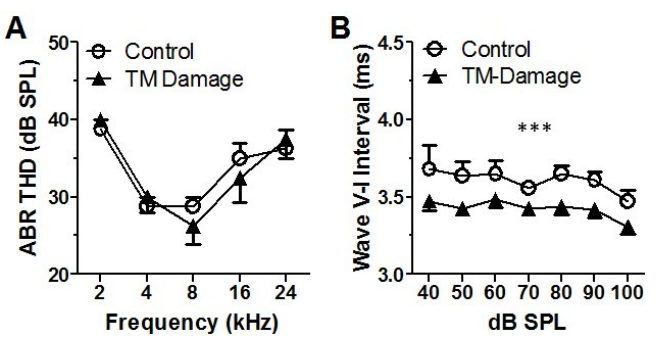

Figure 5. Early age tympanic membrane (TM) damage affected the auditory brainstem response (ABR). (A) Several weeks after the TM damage, the ABR threshold completely recovered. (B) The latency between wave V and Wave I in the TM damaged ears was significantly shorter than the control ears.

To further investigate neural transmission changes in the central auditory system caused by early age hearing loss, we used c-Fos protein staining, an immediate early gene product that is used to mark cell activation and to measure the neural excitability of the central auditory system caused by noise exposure. We collected the brain tissue harvested from 6-8 weeks old rats from both groups after one hour of noise exposure (95 dB SPL, white noise). Figure 6B shows examples of c-Fos staining in a control rat (A) and a damaged membrane rat. Strong c-Fos staining can be seen in the IC of the damaged membrane rat, whereas only scattered c-Fos positive nuclei can be found in the control rat[21]. The average number of c-Fos positive nuclei in the ICs of the damaged membrane rats was significantly higher than that of the control rats. The c-Fos staining in the cochlear nucleus and the auditory cortex were either absent or very light in both groups. These results are similar to the results seen in mice genetically prone to audiogenic seizures[9,10]. This relation suggests that early age tympanic membrane damage can cause sound-evoked hyperexcitability in the IC, which may increase one's susceptibility to audiogenic seizures. In addition, audiogenic seizures can be suppressed by the treatment of vigabatrin, an antiepileptic drug which can increase the ambient GABA concentration in the brain[26]. Acute injections (250 mg/kg) or oral intakes (60 mg/kg/day for 7 days) can inhibit audiogenic seizures[21]. Two weeks after stopping vigabatrin treatments, audiogenic seizure can be induced again using the same procedure. Therefore, these data suggest that audiogenic seizure caused by tympanic membrane damage is related to a lack of GABAergic inhibition.

Conclusion

Although sensorineural hearing loss from noise exposure and ototoxic drugs has traditionally been thought of as an exclusively cochlear phenomenon, there is growing evidence to show that cochlear pathology leads to an excess of functional changes at multiple sites along the auditory pathway. A common theme that emerges from these studies is that cochlear damage, which reduces the neural output of the cochlea, often leads to sound evoked hyperactivity along the auditory pathway, particularly at the inferior colliculus. Surprisingly, noise-induced cochlear damage has a significant impact on cell proliferation and neurogenesis in the hippocampus, a region of the brain involved in spatial navigation and memory. The inescapable conclusion is that hearing loss not only affects the cochlea, but also has profound effects on the central nervous system.

Acknowledgements

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